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(54) Title: MEDICAMENT FOR PREVENTIVE AND THERAPEUTIC TREATMENT OF INFLAMMATORY DISEASES

(57) Abstract

Medicament for preventive and therapeutic treatment of inflammatory diseases which comprises as an active ingredient a substance selected from the group consisting of carvedilol, optically active isomers thereof, its hydroxy–carbazole derivatives and pharmacologically acceptable salts thereof.

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MEDICAMENT FOR PREVENTIVE AND THERAPEUTIC TREATMENT OF INFLAMMATORY DISEASES

BACKGROUND OF THE INVENTION

Technical Field

The present invention relates to a medicament. More specifically, it relates to a medicament useful for therapeutic and/or preventive treatment of inflammatory diseases.

Related Art

Inflammation is a mechanism of presenting lesions including circulatory disturbance, exudation. degeneration, and necrosis by a living body at a stimulated position, in response to stimulations such physical and chemical stimulations, or microbial infection which may cause functional or structural failure of organs and tissues, and eliminating the stimulation to achieve functional and structural regeneration. Diseases accompanied by inflammation are generally referred to as inflammatory diseases. Among inflammatory diseases, myocarditis is a series of diseases in which myocardial damage is caused by inflammation of mycoardium. While its prognosis is relatively good when patients are completely recovered from acute stage, it sometimes progresses to chronic state with repetition of increments and arrests of inflammation, and further advances to dilated cardiomyopathy. The dilated cardiomyopathy is an intractable disease, i.e., a half of the patients die within 5 years after onset, and patients suffering from this disease account for a half of heart transplantation patients in Europe and the United States. Therefore, it is extremely important to treat acut myocarditis for immediate recovery from its acute

stage, and prevent it from progressing to chronic or intractable state (as for dilated cardiomyopathy and myocarditis, see, for example, "Integrated Handbook of Internal Medicine", Vol. 32, "Cardiomyopathy and Myocarditis", published by Nakayama Shoten Co., Ltd., pp. 3 - 9 and pp. 347 - 351). It is suggested that viral infection participates in acute myocarditis. However, from a pathological view concerning inflammation, necrosis of myocardial tissues and infiltration of inflammatory cells to heart are recognized in experimentel model of myocarditis in mice, and therefore, it is considered that cytotoxic effect is caused through immune reactions.

For myocarditis, no therapeutic method that can achieve satisfactory curative effect has been established, and any effective therapeutic medicament has not been developed so far to date. Steroids are symptomatically applied to inflammation. However, steroids may likely advance the infection of myocarditis accompanied with possible viral infection. In addition, stron adverse effects of steroids, per se, are serious problems in therapeutic treatments. Therapeutic effectiveness of antiserum containing specific antibodies and preventive effectiveness of vaccines have been experimentally revealed in view of the possibility of viral infection. However, these methods are considered clinically impractical as it is difficult to identify causative viruses. Furthermore, it fails to achieve effective curative effect against inflammation of myocardium, per se. Accordingly, development of medicaments has been strongly desired which can arrest or completely cure myocarditis and prevent progress and aggravation of myocarditis by inhibiting necrosis of myocardial cells and infiltration of inflammatory cells to heart in myocarditis.

Carbazolyl-(4)-oxy-propanolamine derivatives having vasodilating and antihypertensive activities are known, and their activities have been clarified to be based on ß-blocking actions (EP-A-0 004 920). It is also known that their optically active isomers have similar activities (EP-A-0 127 099). Carvedilol, a typical compound among these compounds, i.e., [(±)-1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]2-propanol], has already been widely used clinically for the treatments of hypertension and stenocardia (trade name: Dilatrend, manufactured and sold by Boehringer Mannheim GmbH). However, therapeutic or preventive effect of this medicament for myocarditis has not been reported so far.

An object of the present invention is to provide a medicament useful for preventive and/or therapeutic treatment of inflammatory diseases, preferably inflammatory diseases, in particular myocarditis. Another object of the present invention is to provide a medicament useful for preventive and/or therapeutic treatment of myocarditis, which exhibits an activity of reducing or eliminating necrosis of myocardial cells and infiltration of inflammatory cells to heart in myocarditis.

SUMMARY OF THE INVENTION

The inventor of the present invention conducted various researches to achieve the foregoing objects. As a result, he found that, when (±)-1-(carbazole-4-yloxy)-3[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol was administered to a mouse myocarditis model inoculated with Encephalomyocarditis (EMC) virus, necrosis of myocardial cells and infiltration of inflammatory cells to normal heart tissues were inhibited and pathological findings of myocarditis were remarkably improved. The present invention was achieved on the basis of these findings.

The present invention thus provides a medicament for preventive and/or therapeutic treatment of inflammatory diseases, which comprises, as an active ingredient, a substance selected from the group consisting of 1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, optically active isomers thereof, its hydroxy-carbazole derivatives and pharmacologically acceptable salts thereof. According to preferred embodiments of the present invention, there are provided; the aforementioned medicament for preventive and/or therapeutic treatment wherein the inflammatory disease is an inflammatory heart disease; the aforementioned medicament for preventive and/or therapeutic treatment wherein the inflammatory heart disease is myocarditis; and the aforementioned medicament for preventive and/or therapeutic treatment which has activity of reducing or eliminating necrosis of cells in inflammatory tissues and/or infiltration of inflammatory cells to normal tissues.

According to further embodiments of the present invention, there are provided a use of a substance selected from the group consisting of 1-(carbazole-4-yloxy)-3-[[2-(o-

methoxyphenoxy)ethyl]amino]-2-propanol, optically active isomers thereof, its hydroxy-carbazole derivatives and pharmacologically acceptable salts thereof for the manufacture of a medicament for preventive and/or therapeutic treatment of inflammatory diseases comprising the substance as an active ingredient; and a method for preventive and/or therapeutic treatment of inflammatory diseases, preferably inflammatory heart diseases, particularly myocarditis, which comprises the step of administering to a mammal including a humanan effective amount of a substance selected from the group consisting of 1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)-ethyl]amino]-2-propanol, optically active isomers thereof, its hydroxy-carbazole derivatives and pharmacologically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The substances selected from the group consisting of 1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, optically active isomers thereof, its hydroxy-carbazole derivatives and pharmacologically acceptable salts thereof used as the active ingredient of the medicament of the present invention are known, and easily obtained by those skilled in the art. For example, EP-A-0 004 920 specifically discloses, as Example 2, a method for the preparation of the racemate of the compounds mentioned above, and EP-A-0 127 099 specifically discloses optically active isomers thereof. Furthermore, EP-A-0 004 920 and EP-A-0 127 099 also specifically disclose pharmacologically acceptable salts of the compounds. As the active ingredient of the medicament of the present invention, any on or more of racemates, optically active isomers in an optically pure form, any mixtures of the optically active isomers, and physiologically acceptable salts of the compounds can be used. In addition, an hydrates and solvates of these substances may also be used.

The carvedilol derivatives which are hydroxylated at the carbazole ring are described in WO-A-94/12718. A preferred derivative is 1-(3-hydroxy-carbazole-4-yloxy)-3[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol.

The medicament of the present invention has activities of inhibiting necrosis of inflammatory cells and tissues, and of inhibiting infiltration of inflammatory cells to normal tissues, as well as activity of remarkably improving pathological findings of inflammation. Therefore, the medicament of the present invention can be applied as a preventive and/or therapeutic medicament to various inflammatory diseases accompanied by inflammation. For example, as specifically demonstrated in the example below, when the medicament of the present invention is applied to an inflammatory heart disease such as myocarditis, the necrosis of myocardium or the infiltration of inflammatory cells to normal heart tissues are remarkably inhibited. Accordingly, inflammatory heart diseases are preferred diseases to which the medicament of the present invention can be applied. An example of inflammatory heart disease includes acute myocarditis, and examples thereof also include chronic myocarditis advanced from acute myocarditis, dilated cardiomyopathy progressed from acute myocarditis. Acute myocarditis include, for example, idiopathic myocarditis which is usually classified as noncausal diseases, and viral myocarditis in which viral infection is directly or indirectly verified. The medicament of the present invention can be used for preventive and/or therapeutic treatment of inflammatory diseases of mammals including humans.

Although the substance mentioned above, per se, may be used as the medicament of the present invention, it is usually preferred that a pharmaceutical composition containing the above substance as an active ingredient is formulated by using one or more pharmaceutical additives available to those skilled in the art. Examples of pharmacologically and pharmacologically acceptable additives include excipients, disintegrating agents or disintegrating aids, binders, lubricants, coating agents, coloring matters, diluents, base materials, dissolving agents or dissolving aids, isotonic agents, pH modifiers, stabilizers, propellants, adhesives and the like. Examples of the formulation suitable for oral administration include tablets, capsules, fine granules, granules, liquids, syrups and the like. Examples of the formulations suitable for parenteral administration include injections, drip infusions, suppositories, inhalants, transmucosal preparation, transdermal preparation, nasal drops, ear drops, patches and the like.

Pharmaceutical preparations suitable for oral, transdermal or transmucosal administrations may contain, as pharmacologically or pharmacologically acceptable additives, for example, excipients such as glucose; disintegrating agents or disintegrating aids such as carboxymethylcellulose; binders such as hydroxymethylcellulose; lubricants such as magnesium stearate; coating agents such as hydroxypropylmethylcellulose; base materials such as vaseline and the like. In addition. as pharmaceutical additives, propellants such as compressed gases; thickeners such as sodium polyacrylate; base cloths such as cotton cloth and the like can also be used. Pharmaceutical preparations suitable for injections and drip infusions may contain, as pharmaceutical additives, aqueous mediums such as distilled water for injection: dissolving agents or dissolving aids which can be contained in injections dissolved before use; isotonic agents such as glucose; pH modifiers such as inorganic acids, organic acids, inorganic bases, and organic bases.

A pharmaceutical preparation containing the particularly preferred active ingredient of the medicament of the present invention, i.e., carvedilol [(±)-1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol], has already been widely used in the clinical filed as ethical medicaments for hypertension and angina pectoris (trade name: Dilatrend, manufactured and sold by Boehringer Mannheim GmbH). Therefore, this pharmaceutical product, per se, may be used as the medicament of the present invention. Administration dose of the medicament of the present invention should be varied depending on various factors including the sorts of applicable inflammatory diseases, conditions and age of patients, purpose of prevention or therapeutic treatment and the like, and can be suitably selected by those skilled in the art by considering these factors. It has been already varified that the preferred active ingredient of the medicament of the present invention, carvedilol, is a highly safe substance as used clinically.

EXAMPLES

The present invention will be further explained more specifically by referring to the following examples. However, the scope of the invention is not limited to these examples. In the example, carvedilol [(±)-1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol] was used as the medicament of the present invention,

and compared with metoprolol [1-(isopropylamino)-3-[p-(ß-methoxyethyl)phenoxy]-2-propanol tartrate], which is known as a compound also having ß-receptor blocking activity.

Example 1:

Inhibitory activity of carvedilol on necrosis of myocardium and on infiltration of inflammatory cells to heart, and its improving activity on pathological findings of inflammation in mouse myocarditis model

Carvedilol (Daiichi Pharmaceutical Co., Ltd.) or metoprolol (Sigma Chemical Co.) was dissolved in phosphate buffered saline (PBS) containing 1% methylcellulose for the use of this experiment. As EMC virus for inoculation, M variant (obtained from American Type Culture Collection) was used, and the concentration was adjusted to 100 pfu/ml (pfu: plaque forming unit) with Eagle MEM culture medium (EMEM: Nissui Pharmaceutical Co., Ltd.) before use. Each of 4-week old DBA/2 male mice in three groups was intraperitoneally inoculated with 0.1 ml of the EMC virus (10 pfu/mouse). From the day of the inoculation, the mice were orally administered with a test compound at the doses set out below every single day.

Test group:	10 mg/kg body weight of carvedilol
Comparative group:	30 mg/kg body weight of metoprolol
Control group:	PBS

On the seventh day, the hearts were isolated from survived mice, and the hearts were bled and washed with PBS. Then the tissues were fixed with 10% formalin to prepare paraffin embedding sections. Sample sections were prepared and stained with hematoxylin and eosin, and histopathological findings were observed. The viral myocarditis mice were prepared according to the method of Matsumori et al. (Matsumori, A. and Kawai, C., Circulation, 66, pp. 355 - 360, 1982).

Under microscopic observation, the rates of myocardial necrosis image or inflammatory cell infiltration image in left ventricle brachyaxis sectional images were classified into 0

(no damage); 1 (less than 25 %); 2 (25 % or more, less than 50 %); 3 (50 % or more, less than 75 %); and 4 (75 % or more, 100 % or less). Observation was independently performed by two observers, and then evaluations by the two were averaged to give the evaluation value for an individual mouse. The results obtained were statistically analyzed by the variance analysis (ANOVA) method based on the multiplex comparison method of Bonferroni, and when $p < 0.05$, it was judged that there was statistically significant difference. For each of the 3 groups, 9 mice were finally used for the analysis. There was no significant difference between the compative group and the control group as to both of necrosis of myocardium and infiltration of inflammatory cells, whereas both of necrosis of myocardium and infiltration of inflammatory cells were significantly inhibited in the test group compared to the control group, and remarkable improvements of these pathological findings were recognized. Metoprolol, which also has ß-receptor blocking activity like carvedilol, showed no inhibition on necrosis of myocardium and on infiltration of inflammatory cells to heart, as well as no improvement of pathological findings of inflammation. The results are shown in Table 1.

Table 1

	N	Necrosis of myocardium	Infiltration of Inflammatory cells
Test group	9	1.4 ± 0.2*	1.4 ± 0.2*
Comparison group	9	2.1 ± 0.8	1.9 ± 0.3
Control group	9	2.1 ± 0.2	2.1 ± 0.2

(Mean ± Standard error)

* $p < 0.05$ vs. Control group

The medicament of the present invention has the activity of inhibiting necrosis of inflammatory tissues or cells, and also has activity of inhibiting infiltration of

inflammatory cells. Therefore, the medicament is useful for preventive and/or therapeutic treatment of various inflammatory diseases accompanied by inflammation, for example, myocarditis.

WHAT IS CLAIMED IS:

1. Use of a substance selected from the group consisting of 1-(carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethly]amino]-2-propanol, optically active isomers thereof, its hydroxy-carbazole derivatives and pharmacologically acceptable salts thereof as an active ingredient for the preparation of a medicament for preventive and/or therapeutic treatment of inflammatory diseases.

2. The use according to claim 1, wherein the active ingredient is carvedilol.

3 The use according to claim 1, wherein the active ingredient is 1-(3-hydroxy-carbazole-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol.

4. The use of the medicament according to claims 1 to 3, wherein the inflammatory disease is an inflammatory heart disease.

5. The use of the medicament according to claim 4, wherein the inflammatory heart disease is myocarditis.

6. The use according to any one of claims 1 to 5, wherein the active ingredient has an activity of reducing or eliminating necrosis of tissues in inflammatory tissues and/or reducing or eliminating infiltration of inflammatory cells to normal tissues.